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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,191	10/03/2003	Randall T. Moon	UWOTL121818	1034

26389 7590 10/11/2006

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/679,191	MOON ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-33* is/are pending in the application.

4a) Of the above claim(s) *15-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-14 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: alignment us-10-679-191a-1_copy_3005_4336.rni.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 3 October 2003, which claims benefit of US provisional application 60/416,504, filed 3 October 2002. The preliminary amendment filed 28 July 2006 has been entered. Claims 1-29 were originally filed. Claims 1-8 were canceled, claims 9, 11, 15-17 and 22-24 were amended and claims 30-33 were added in the 28 July submission. Claims 9-33 are presently pending.

Election/Restrictions

Applicant's election of Group II (claims 9-14 and 30-33) in the reply filed on 28 July 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 15-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the 28 July reply.

Claim Construction

The instant claims, are directed to a host cell or transgenic zebrafish comprising a reporter nucleic acid, wherein the reporter nucleic acid might have as little as 80% identity to "a first DNA molecule" comprising nucleotides 3005-4336 of SEQ ID NO: 1 contiguous to nucleotides 1-243 of SEQ ID NO: 1. It is first noted that the "first DNA molecule" used as a reference sequence is recited using open language. This problematic for claim construction

because what is claimed is defined based on similarity to undefined sequence. For the sake of illustration, consider a claim to a nucleic acid comprising 80% identity to a nucleic acid comprising a specific 100 base sequence. This claim covers any nucleic acid that is 80% identical to any nucleic acid that comprises the 100 base sequence. Therefore, if the 100 base sequence is present in a vector consisting of 900 base pairs, the claim covers the vector independent of the defined 100 base sequence because you can remove the defined sequence and still have a nucleic acid that is >80% identical to the sequence that comprised the defined sequence. As another example, it is noted that in the instant case the application discloses SEQ ID NO: 1, which is a nucleic acid comprising nucleotides 3005-4336 of SEQ ID NO: 1 contiguous to nucleotides 1-243 of SEQ ID NO: 1 the in a prior art vector pCS2+. The prior art vector constitutes approximately 65% of the total SEQ ID NO: 1. Therefore, a claim to a nucleic acid comprising 65% identity with the "first DNA molecule" (i.e., SEQ ID NO: 1) would encompass the pCS2+ vector itself. Although the claim recites that the nucleic acid having 80% identity "has the same reporter function as said first DNA molecule", the claim does not specify a particular reporter activity for the first DNA molecule. Therefore, the activity could be any reporter activity that might be comprised by any nucleic acid molecule. For example, the pCS2+ vector comprises selectable marker genes, which can be used as a reporter for the presence of the vector in the cell. Therefore, defining the nucleic acid of the claims as 80% identical to a nucleic acid that is open to comprising any sequence and having any reporter activity that might be comprised by the sequence results in a claim of tremendous and essentially indeterminable scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-14 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The scope of the claimed invention is described herein above. It is further noted that the claims also embrace essentially any modification of the promoter and reporter gene sequences explicitly disclosed in the application. Thus, in addition to encompassing a vast genus of undefined sequences, the claims are also directed to a broad genus of reporter nucleic acids having the reporter function reduced to practice in the application.

The Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the

genus" (Federal Register, Vol. 66, No. 4, Column 3, page 1106). "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (MPEP §2163(3)(a)(ii)).

The Guidelines further state, "[s]atisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the genus in view of the species disclosed" (*Id.* at 1106, column 3).

In the instant case, the application discloses a single first DNA molecule comprising a fragment of the TOPFlash vector (nucleotides 3005-4336 of SEQ ID NO: 1) containing the TCF/Lef responsive promoter, which is operably linked to a destabilized GFP reporter gene (referred to in the instant application as d2GFP; nucleotides 3485-4327 of SEQ ID NO: 1). Further, the specification teaches that nucleotides 1-243 comprise the SV40 polyA signal. (See especially the brief description of Figure 1 at p. 5.)

The specification teaches that the nucleic acid comprising nucleotides 3005-4336 of SEQ ID NO: 1 has a reporter function which provides for quantitative assessment of β-catenin and Lef dependent transcription. (See especially p. 8, ¶2 and p. 28, ¶3.) However, as discussed above, although the claim recites that the nucleic acid having 80% identity with the first DNA molecule "has the same reporter function as said first DNA molecule", the claim itself does not specify a

particular reporter activity for any of the nucleic acids of the claims. Thus, the claim is open to nucleic acids having any reporter activity, not only reporter activity as a measure of β-catenin and Lef dependent transcription. The application clearly fails to describe a genus representative of such breadth.

Furthermore, even if one were to assume, *arguendo*, that the function referred to in the claims is a reporter of β-catenin and Lef dependent transcription, the single species disclosed in the application is not representative of the broad genus claimed because it does not convey the necessary common attributes or features of any nucleic acid having the recited function.

With regard to the "relevant identifying characteristics" of the claimed invention, the specification provides no disclosure of the structural features that define the function of a reporter of β-catenin and Lef dependent transcription. As stated in MPEP 2163(I)(A), a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes. Thus, applications that seek to claim biological molecules having a defined function and broadly divergent structure must disclose a correlation between that function and a corresponding structure. No such correlation is disclosed in the instant case and, therefore, the application also fails to provide the relevant identifying characteristics of the claimed invention.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention because it does not provide adequate written description for the broad class of any nucleic acid having 80% identity with any molecule comprising the sequence recited in the claim

and the "same reporter function" of any DNA molecule comprising the recited sequence. Therefore, the claims are properly rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description.

Claims 9-14 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell and transgenic zebrafish comprising a DNA molecule comprising nucleotides 3005-4336 of SEQ ID NO: 1 contiguous to nucleotides 1-243 of SEQ ID NO: 1, wherein the nucleic acid functions as a reporter of β-catenin and Lef dependent transcription, does not reasonably provide enablement for the broad scope of what is presently claimed. (See supra.) The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claims, construed as discussed herein above, embrace a vast genus of undefined sequences or, construed more

narrowly in the interest of compact prosecution, are directed to a broad genus of reporter nucleic acids having the reporter function reduced to practice in the application.

State of the prior art and level of predictability in the art: The art teaches that the functional determinants of any given promoter molecule are complex, and that the effect of modifying any given nucleic acid in a promoter sequence is not readily predicted.

The art teaches repeatedly that mutations in a critical region of a promoter element can destroy the ability of a construct to function in promotion. For example, Pietrzkowski *et al.* (1991)) *Exp. Cell Res.* 193:283-290 teaches that when synthetic promoters were produced wherein the sequence of an enhancer element was mutated, little to no promotion was observed from the mutant constructs (see for example Figure 6). Chan *et al.* (2001) *Plant Mol. Biol.* 46 :131-141 teaches that mutation in a critical XXIII element of the GAPB promoter abolished transcription completely (Figure 6), while mutations in other elements did not abolish activity (Figure 6). Thus, it is evident that it is highly unpredictable how promoter elements will respond to even very minor sequences changes. In addition, the order that promoter elements occur in a construct has an effect on the functionality of the promoter. Omilli *et al.* (1986) *Mol. Cell Biol.* 6:1875-1885 teaches that the relative arrangement of promoter elements is a critical factor contributing to the activity of the promoter (ABSTRACT, for example).

According to the teachings of Arnone *et al.* (1997) *Development* 124:1851-1864, the critical functional elements of the nucleic acid molecule of the claims might be considered a regulatory module. Arnone *et al.* teaches that individual regulatory modules are always found to contain multiple transcription factor target sites, and these contribute in various ways to the overall regulatory output (paragraph bridging pages 1851-1852). Arnone *et al.* further teaches

that an underestimate of the number of diverse transcription factor interactions found within regulatory modules is approximately 6.2 (first full paragraph on page 1853). Still further, Arnone *et al.* teaches, "[t]here are no examples of regulatory modules serviced only by homeodomain proteins, or Zn finger proteins, and so forth. This suggests diversity in the nature of the protein:protein interactions that are required of the factors in order for each module to generate and communicate its regulatory output" (second full paragraph on page 1853). Thus, Arnone *et al.* teaches that promoters are comprised of a variety of regulatory elements which work in concert to provide the functional characteristics of any given promoter.

Amount of direction provided by the inventor and existence of working examples: In the instant case, the application discloses a single first DNA molecule comprising a fragment of the TOPFlash vector (nucleotides 3005-4336 of SEQ ID NO: 1) containing the TCF/Lef responsive promoter, which is operably linked to a destabilized GFP reporter gene (referred to in the instant application as d2GFP; nucleotides 3485-4327 of SEQ ID NO: 1). Further, the specification teaches that nucleotides 1-243 comprise the SV40 polyA signal. (See especially the brief description of Figure 1 at p. 5.) The specification teaches that the nucleic acid comprising nucleotides 3005-4336 of SEQ ID NO: 1 has a reporter function which provides for quantitative assessment of β-catenin and Lef dependent transcription. (See especially p. 8, ¶2 and p. 28, ¶3.) However, the application includes no teachings as to how the disclosed sequences might be modified while maintaining "the same reporter function".

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, making the claimed invention would require undue experimentation. According to the broadest reasonable construction, the

claims encompass cells and zebrafish comprising a broad genus of structurally and functionally undefined DNA molecules. According to a more narrow construction, the claims are directed to a genus of cells and zebrafish comprising nucleic acids having broadly recited structural limitations. However, neither the relevant art nor the instant disclosure identifies the structural elements required to provide the function contemplated in the specification. Thus, the skilled artisan would not be able to distinguish the operative embodiments of the claimed invention from those that are inoperative without having to resort to empirical experimentation. Although the presence of inoperative embodiments within the scope of the claim does not necessarily render a claim non-enabled (see *Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414). *Atlas* also provides, "[o]f course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid" (page 414). In the instant case, the structural limitations recited in the claims encompass many thousands of possible combinations, and many, if not most of these combinations would be inoperative. As identifying the operative embodiments within the scope of the claims would require a large amount of empirical experimentation, the amount of experimentation required to make the full scope of the claimed invention would clearly be undue.

In view of the foregoing, the skilled artisan would conclude, based on the unpredictable nature of the art and the failure of the instant disclosure to teach how to make a DNA molecule commensurate with the broad scope of the claims, that the specification is not enabling for what is presently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-14 and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As described above, the claims are directed to cells or zebrafish comprising a nucleic acid that is defined as having 80% identity to and the same reporter function as a DNA molecule comprising essentially unlimited undefined sequence. As written, it is not possible to definitively determine what is within the scope of the nucleic acid of the claims and, therefore, the metes and bounds of the claims as a whole are unclear. It is suggested that any recitation of % identity explicitly identify the reference sequence. For example, "comprising a sequence 80% identical to the nucleotide sequence 3005-4336 of SEQ ID NO: 1".

Claims 13 and 14 are indefinite in reciting "the mutation". There is no antecedent basis for a mutation in claim 11, from which the claims depend. Amending the claims to depend from claim 12 would be remedial.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 9-11, 30 and 31 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Dorsky et al. (2002) *Dev. Biol.* 241:229-237. (Published online 28 February 2002).

Dorsky et al. is Applicant's own prior art disclosure of the construction of the TOPdGFP vector and the transgenic zebrafish reduced to practice in the instant application. (See, *e.g.* the "MATERIALS AND METHODS" section commencing on p. 230, Figures 1 and 2 and the captions thereto.) The cells and transgenic zebrafish of Dorsky et al. clearly anticipate the cell and zebrafish of the instant claims. Furthermore, as the prior art publication names an author that is not named as an inventor on the instant application, the disclosure of Dorsky et al. is by another and qualifies as prior art under 35 USC §102(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dorsky et al. (*supra*) in view of Talbot et al. (2000) *Genes Dev.* 14:755-762.

The teachings of Dorsky et al. as applied to claim 11 are discussed herein above. Dorsky et al. does not teach that the transgenic zebrafish disclosed therein should comprise an induced mutation, wherein the mutation is induced by chemical mutagenesis or by insertional retrovirus mutagenesis as recited in claims 12-14. However, Dorsky et al. does teach that the zebrafish "provides an easy assay...to screen for mutations or molecules that can disrupt Wnt/β-catenin signaling". (P. 236, ¶3, final sentence.) Thus, Dorsky et al. clearly suggests using a transgenic zebrafish having the limitations of the claimed zebrafish to assay for mutations that affect Wnt/β-catenin signaling.

In the section entitled, "Insertional mutagenesis" beginning on p. 757, Talbot et al. discusses the use of chemical and insertional retrovirus mutagenesis in zebrafish for the purpose of genomic analysis as contemplated by Dorsky et al. Talbot et al. teaches advantages and disadvantages of each method and concludes, "For now it seems clear that it is the power of the

two methods together, chemical and insertional mutagenesis, that will advance the zebrafish field most rapidly in the near future." (P. 758, col. 2, ¶2.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use chemical and/or insertional retroviral mutagenesis as taught by Talbot et al. to assay for mutations that affect Wnt/β-catenin signaling as contemplated by Dorsky et al. One would be motivated to use either or both of the mutagenesis techniques taught by Talbot et al. (i.e., chemical and insertional mutagenesis) in the method of assaying for mutations in view of the teachings of Talbot et al. indicating that the methods are powerful tools for inducing mutations in zebrafish.

Absent evidence to the contrary, one would have a reasonable expectation of success in using the method of Talbot et al. in the analysis contemplated by Dorsky et al. in view of the teaching therein that both chemical and insertional mutagenesis had already proved useful in zebrafish. (See, e.g., p. 758, col. 2, ¶2.)

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Korinek et al. (1997) *Science* 275:1784-1787 in view of Li et al. (2000) US Patent No. 6,130,313.

The claim is directed to a host cell transformed with a reporter nucleic acid comprising a DNA molecule 80% identical to a DNA molecule comprising nucleotides 3005-4336 of SEQ ID NO: 1 contiguous to nucleotides 1-243 of SEQ ID NO: 1. As discussed above, the claims, as

written, are broad and indefinite. However, it is presumed to be applicant's intention that the claims be limited to a cell comprising a nucleic acid molecule comprising 80% identity with the nucleotide sequence 3005-4336 of SEQ ID NO: 1 contiguous with nucleotides 1-243 of SEQ ID NO: 1. If the claims were so limited, the nucleic acid of the claims would read on a nucleic acid comprising approximately 95% identity with the sequence 3005-4336 of SEQ ID NO: 1. This is because the 244 nucleotide fragment represents approximately 15% of the whole and therefore can be completely deleted within the scope of 80% identity. Furthermore, even with the deletion of the 244 nucleotide fragment, the claim allows for 5% variation within the remaining sequence.

The specification teaches that the sequence 3005-4336 is comprised of the promoter/enhancer region of the reporter vector pTOPFLASH fused to a nucleic acid encoding a destabilized GFP reporter gene (d2GFP). (See especially the ¶ bridging pp. 23-24 of the instant specification.)

Korinek et al. teach the construction of the pTOPFLASH vector comprising the promoter/enhancer region fused to a luciferase reporter gene. (See especially p. 1786, ll. 2-10.) Korinek et al. further teaches the use of the pTOPFLASH vector in cellular assays for β-catenin and TCF activity. (See especially Fig. 3 and the caption thereto.) In footnote 14, Korinek et al. teaches that these assays required various manipulations including harvesting and lysis of cells for the detection of reporter gene expression.

Li et al. teaches a rapidly degrading GFP-fusion protein having improved properties for reporter gene assays. A nucleic acid encoding said rapidly degrading GFP-fusion protein is set forth in SEQ ID NO: 2 of Li. et al., which is 100% identical to a portion of the nucleic acid

sequence consisting of nucleotides 3005-4336 of the instant SEQ ID NO: 1. (See the attached alignment us-10-679-191a-1_copy_3005_4336.rni.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the nucleic acid encoding the rapidly degrading GFP molecule of Li et al. for the luciferase encoding nucleic acid in the pTOPFLASH vector of Korinek et al. Motivation to do so is found in the nature of the problem solved by the TOPFLASH vector, which is to provide a reporter of gene expression in intact cells and the advantages of the rapidly degrading GFP as taught by Li et al. Li et al. teaches that GFP has several advantages over other reporter genes known in the art such as allowing for fluorescence detection intracellularly without performing additional expensive steps; e.g. lysing cells, adding exogenous substrates or cofactors, fixing the cell preparation, etc. (See col. 4, ll. 15-20.) Furthermore, Li et al. teaches that the rapid turnover version of GFP has several advantages over other GFP's including less toxicity, decreased assay interference by GFP accumulation, and ability to assay transient gene expression.

In view of the advantages of GFP in general and rapid turnover GFP in particular taught by Li et al., the skilled artisan would clearly be motivated to replace the luciferase reporter with the GFP reporter of Li et al. Absent evidence to the contrary, one would have a reasonable expectation of success in combining the elements of the prior art because GFP is a well established reporter that has been used in a wide variety of gene expression assays.

Thus, at the time the invention was made it would have been obvious to one of ordinary skill in the art to place a sequence that is 100% identical to the reporter gene comprised within the 3005-4336 fragment recited in the instant claims into the pTOPFLASH such that expression

of the reporter is under the control of the promoter/enhancer comprised within said 3005-4336 fragment. Although the resultant construct might be greater or lesser than 95% identical to the 3005-4336 fragment depending upon how much superfluous sequence is comprised between the promoter/enhancer and the reporter gene coding sequence, the presence of such sequence would not distinguish a construct from what is claimed. MPEP 2144.09 states, "A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities." Given the art, the skilled artisan would be motivated to construct the nucleic acid such that the promoter/enhancer drives expression of the GFP reporter and, therefore, would not include sequence that materially changes the reporter function of the construct. Even if the end product comprised sufficient superfluous sequence between the promoter/enhancer and the reporter to render the construct less than 95% identical to the 3005-4336 fragment, the critical functional elements of the construct would still be 100% identical to the functional elements comprised by the 3005-4336 fragment and the construct would have the same functional properties as the fragment. In view of this, even combining the elements as suggested by the art such that a sequence having less than 95% identity with the 3005-4336 fragment resulted would still render obvious what is presently claimed.

For these reasons, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC §103(a) as obvious over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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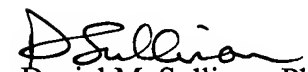

Daniel M. Sullivan, Ph.D.
Primary Examiner
Art Unit 1636

us-10-679-191a-1_copy_3005_4336.rni

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RESULT 1
US-09-062-102-2
; Sequence 2, Application US/09062102
; Patent No. 6130313
; GENERAL INFORMATION:
;  APPLICANT: Kain, Steve
;  APPLICANT: Li, Xianqiang
;  TITLE OF INVENTION: Rapidly Degrading GFP-Fusion Proteins and Methods
;  TITLE OF INVENTION: of Use
;  FILE REFERENCE: D6100
;  CURRENT APPLICATION NUMBER: US/09/062,102
;  CURRENT FILING DATE: 1998-04-17
;  EARLIER APPLICATION NUMBER: US 60/060,855
;  EARLIER FILING DATE: 1997-10-02
;  NUMBER OF SEQ ID NOS: 3
; SEQ ID NO 2
;   LENGTH: 850
;   TYPE: DNA
;   ORGANISM: artificial sequence
;   FEATURE:
;   OTHER INFORMATION: DNA sequence which encodes the EGFP-MODC422-461
;   OTHER INFORMATION: fusion protein.
US-09-062-102-2

  Query Match             63.8%;  Score 850;  DB 3;  Length 850;
  Best Local Similarity   100.0%;  Pred. No. 6.2e-171;
  Matches  850;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy        481 ATGGTGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGAC 540
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